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Background Paper on the Neurobiology of Nicotine Addiction

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Background paper on the neurobiology of nicotine addiction

Since the 1980s, it has become increasingly recognized by clinicians, researchers, and public health experts that tobacco products are appropriately categorized among the most addictive and deadly of all dependence producing substances (World Health Organization 2001; Royal College of Physicians of London 2000). There are over 4000 chemicals in cigarette smoke, many of which could potentially contribute to the addictive properties of tobacco. In light of myriad preclinical studies demonstrating nicotine's reinforcing properties in many species including humans (Goldberg et al. 1981; Risner & Goldberg 1983; Goldberg & Henningfield 1988; Corrigall & Coen 1991; Fudala et al. 1985; Huston-Lyons & Kornetsky 1992; Watkins et al. 1999; Markou & Paterson 2001), there is little debate about the fact that people smoke primarily to experience the acute psychopharmacological properties of nicotine, and that nicotine is one of the major components in tobacco smoke responsible for addiction (Balfour 1984; USDHHS 1988; Royal Society of Canada 1989; Stolerman 1991; Stolerman & Jarvis 1995; Royal College of Physicians of London 2000). Nevertheless, in addition to nicotine, there are other factors that contribute to the tobacco smoking habit, as suggested by the fact that tobacco craving is only partially relieved by administration of pure nicotine forms. These other factors include sensory (e.g., smell and taste of cigarettes) and conditioned stimuli (e.g., the sight of other people smoking, tobacco advertisements), as well as other ingredients in tobacco smoke (e.g., tar) that may have synergistic effects with nicotine (Butschsky et al. 1995; Rose et al. 1993; Shahan et al. 1999; Crooks & Dwoskin 1997; Jacob et al. 1999; Bardo et al. 1999; Caggiula et al. 2001a, 2001b; Perkins et al. 2001). Thus, it is important to emphasize here that although pure nicotine can serve as a positive reinforcer, it does not mean that the reinforcing effects of cigarette smoke are fully accounted for by nicotine. As indicated above, sensory effects of tobacco can acquire conditioned reinforcing properties. In addition, other chemicals present in smoke can interact with nicotine to enhance nicotine's reinforcing effects by either having their own primary pharmacological effects, in addition to potentially influencing nicotine dose delivered and absorbed, and the speed of nicotine delivery. For example, Philip Morris researchers found that acetaldehyde (which is present in cigarette smoke) can serve as a reinforcer in its own right for animals (DeNobel & Mele as reported by the U.S. Food and Drug Administration 1996; Royal

College of Physicians of London 2000). Further, these investigators found that when nicotine and acetaldehyde were administered simultaneously, the reinforcing effects were stronger than those produced by either drug alone. Other substances also have been investigated such as the tobacco alkaloid and active nicotine metabolite nornicotine which is self-administered in rats (Bardo et al. 1999), and which also produces psychomotor stimulant and discriminative stimulus effects (Bardo et al. 1997; Dwoskin et al. 1999). Such work has important implications for understanding the powerfully addicting effects of tobacco (Royal College of Physicians of London 2000). The present paper will focus on the neuropharmacology of nicotine, and on the neuronal substrates mediating the reinforcing effects of acute nicotine and nicotine withdrawal partly because in neurobiological research it is important to isolate and study each factor thoroughly before interactions of various factors are investigated, and because nicotine is probably one of the main ingredients in tobacco smoking leading to addiction. Similarly to other major drugs of abuse, it is believed that both the reinforcing properties of nicotine and the nicotine withdrawal syndrome lead to the development and maintenance of the tobacco smoking habit and the precipitation of relapse after a period of abstinence (Wikler 1973; Levine 1974; Stewart et al. 1984; Ludwig 1986; McLellan et al. 1986; Childress et al. 1986, 1988; Shiffman 1989; O'Brien et al. 1990; Koob et al. 1993; Markou et al. 1993, 1998; Hughes & Hatsukami 1992; Watkins et al. 2000a; Kenny & Markou 2001).

Nicotinic Acetylcholine Receptors

Nicotine is an alkaloid that is present in concentrations of about 1-3% in tobacco cultivated for product manufacture (Browne 1990). Nicotine is an agonist at several subpopulations of nicotinic acetylcholine receptors (nAchR; Paterson & Nordberg 2000; Vidal 1996; Henningfield et al. 1996). Nicotinic receptors are expressed on mature skeletal muscle, in autonomic ganglia and within the central nervous system (Holladay et al. 1997). Not surprisingly, most interest in the behavioral actions of nicotine has focused on the role of nAChRs located within the central nervous system. Neuronal nAChRs, similar to other ligand-gated ion channels, are composed of five membrane spanning subunits that combine to form a functional receptor (Albuquerque et al. 1997; Dani 2000; Lindstrom et al. 1996; Lena & Changeux 1998; Role & Berg 1996). Individual neuronal nAChR subunits arrange in different combinations to form individual nAChRs with distinct pharmacological and kinetic properties. The neuronal α subunit exists in nine isoforms (α2-α10) whereas the neuronal ß subunit exists in three isoforms (ß2-ß4) (Elgoyhen et al. 2001; Arneric et al. 1995; Wonnacott 1997). Oocyte expression systems injected with pairwise combinations of different neuronal α and ß subunits have provided evidence that these subunits combine with a stoichiometry of 2α:3ß to produce a functional neuronal nicotinic hetero-oligomeric receptor (Deneris et al. 1991; Conroy & Berg,

1995; Colquhoun & Patrick 1997). In contrast, α7, α8 and α9 subunits form homo-oligomeric complexes composed of five α subunits and lacking ß subunits (Chen et al., 1998), with only the α7 pentamer being expressed in the central nervous system.

Based on radioligand binding studies, neuronal nAChRs have been divided broadly into three classes within the rat brain: those with a high affinity binding site for [^{3}H]-nicotine which correspond to α4-containing nAChRs, the α4ß2 combination being the most abundant (Flores et al. 1992; Picciotto et al. 1995); those with high affinity for [^{125}I]-α-bungarotoxin which correspond to α7 nAChRs (Clarke 1992), and those with high affinity for neuronal bungarotoxin which correspond to α3-containing nAChRs (Schulz et al. 1991). The precise combinations of nAChR subunits that constitute active nAChRs within the CNS *in vivo* are unknown and have so far only been inferred by their pharmacological profile (Kaiser et al. 1998; Luo et al. 1998; Sershen et al. 1997; Sharples et al. 2000). However, with the advent of more sophisticated tools it is becoming possible to identify the nAChR subunits expressed by individual neurons within specific brain regions (Sheffield et al. 2000; Lena et al. 1999).

It has been proposed that the exclusive or predominant role of nAChRs in the brain is the modulation of neurotransmitter release (Wonnacott 1997). Brain nicotinic receptors are situated mainly on presynaptic terminals (Wonnacott 1997) but also are found at somatodendritic, axonal and postsynaptic locations (for review, Sargent 1993). Accordingly, by actions at nAChRs, nicotine stimulates the release of most neurotransmitters throughout the brain (Albuquerque et al. 1997; Alkondon et al. 1997; Gray et al. 1996; McGehee et al. 1995; McGehee & Role 1995; Role & Berg, 1996; Kenny et al. 2000; Araujo et al. 1988; Toide & Arima 1989; Wilkie et al. 1996; Grady et al. 2001). Therefore, as discussed below, it is likely that various neurotransmitter systems are involved in the adaptations that occur in response to chronic nicotine exposure that give rise to dependence and withdrawal responses.

Neurosubstrates of Nicotine Reinforcement

Nicotine is an effective reinforcer for both humans and experimental animals as demonstrated by reports of mild euphoria in humans (Pomerleau & Pomerleau 1992) and intravenous self-administration studies in several species, such as rats, mice, nonhuman primates and humans (e.g., Goldberg et al. 1981, 1983; Henningfield et al 1985; Goldberg & Henningfield, 1988; Corrigall & Coen 1989; Donny et al. 1995; Shoaib et al. 1997; Watkins et al. 1999; Picciotto et al. 1998; Markou & Paterson 2001). The mesolimbic dopaminergic system is considered of importance for the reinforcing properties of acute nicotine (for reviews, Watkins et al. 2000a; Picciotto & Corrigall 2002). Acute nicotine administration increased the firing rate of ventral tegmental area (VTA) dopaminergic neurons (Grenhoff et al. 1986; Pidoplichko et al. 1997), and elevated dialysate dopamine levels specifically in the shell of the nucleus accumbens

(Imperato et al. 1986; Damsma et al. 1989; Mifsud et al. 1989; Benwell & Balfour 1992; Pontieri et al. 1996; Nisell et al. 1997; Carboni et al. 2000), possibly through excitatory actions at nAchRs on mesolimbic dopaminergic neurons at both the VTA and the nucleus accumbens (Nisell et al 1995; Teng et al. 1997; McGehee & Role 1996). Interestingly, nAChRs in the VTA were shown to play a more important role than those in the nucleus accumbens in mediating the effects of nicotine on dopamine release (Nisell et al. 1994a, b, 1997). The role of nAchRs on VTA dopaminergic neurons in nicotine reinforcement is supported by the finding that injections of the competitive nAchR antagonist dihydro-ß-erythroidine (DHßE) (Williams & Robinson 1984) into the VTA (Corrigall et al. 1994), or lesions of the mesolimbic dopaminergic projections with 6-hydroxydopamine (Corrigall et al. 1992) or systemic administration of dopamine receptor antagonists (Corrigall & Coen 1991) decreased nicotine self-administration. Nevertheless, a dopamine receptor antagonist did not reverse nicotine-induced cognitive improvements demonstrating the specificity of the above results to the reinforcing effects of nicotine (Levin 1997; Levin & Simon 1998). Other mechanisms by which nicotine may elevate striatal dopamine levels are through enhancement of frontal cortex glutamatergic stimulation of ventral striatum dopamine release, and/or glutamatergic stimulation of VTA dopaminergic neurons projecting to the striatum. Nicotine increases glutamate release through agonism at excitatory presynaptic nAchRs on glutamatergic terminals (Toth et al. 1992; Vidal & Changeux 1993; Nisell et al. 1995; Radcliffe & Dani 1998; Damaj et al. 1999; Gioanni et al. 1999; Fu et al. 2000). Acute nicotine administration increased the release of glutamate in various brain sites including the VTA (Mansvelder and McGehee, 2000; Fu et al., 2000; Grillner and Svensson, 2000), nucleus accumbens (Reid et al. 2000), prefrontal cortex (Gioanni et al. 1999) and hippocampus (Gray et al. 1996). In terms of the VTA, it is believed that nicotine acts at presynaptic α7 nAChRs located upon glutamate afferents (Mansvelder & McGehee 2000) to increase glutamate release in the VTA which in turn stimulates dopamine release in the nucleus accumbens (Nisell et al. 1994a; 1994b; Schilstrom et al. 1998a, b; Mansvelder & McGehee 2000; Fu et al. 2000). This enhanced glutamate release then acts at *N*-methyl-D-aspartate (NMDA) and non-NMDA receptor sites on postsynaptic dopamine neurons and increases their firing rate. Accordingly, NMDA receptor antagonists blocked tolerance to the locomotor depressant effects of acute nicotine (Shoaib & Stolerman 1992; Shoaib et al. 1994), and sensitization to the locomotor stimulant effects of chronic nicotine (Shoaib & Stolerman 1992). Blockade of postsynaptic metabotropic glutamate receptors 5 led to decreases in nicotine self-administration in rats and mice (Paterson et al. 2003), possibly by decreasing nicotine-stimulated dopamine release in the mesolimbic system. Similar decreases in nicotine self-administration are seen also after administration of dopaminergic and nAchR antagonists (Corrigall & Coen 1989, 1991; Watkins et al. 1999). In terms of nAchRs, several studies suggest an important involvement of the α4ß2 and α7 nAchR subtypes in both the

nicotine-induced release of dopamine and nicotine reinforcement (Picciotto et al. 1998; Schilstrom et al. 1998a; Watkins et al. 1999; Sharples et al. 2000; Grillner & Svensson 2000; Markou & Paterson 2001; however, see Grottick et al. 2000). Both the α4ß2 and α7 subtypes have been implicated also in nicotine's effects on memory (Bancroft & Levin, 2000; Levin et al. 1999), as well as the anxiolytic effects of nicotine (Cheeta et al. 2001; Gordon 1999) that also contribute to persistent tobacco use (USDHHS 1988).

In addition to dopamine and glutamate, another neurotransmitter system that may be critically involved in the reinforcing effects of acute nicotine is γ-aminobutyric acid (GABA). The dopaminergic neurons projecting from the VTA to the nucleus accumbens (Fallon & Moore 1978) receive descending GABAergic input from the ventral pallidum and the nucleus accumbens (Waalas & Fonnum 1979; Sugita et al. 1992). These GABAergic neurons have an inhibitory effect on dopaminergic tone (Klitenick et al. 1992; Engberg et al. 1993) at the level of both the VTA and the nucleus accumbens (Heimer et al. 1991; Heimer & Alheid 1991; Churchill et al. 1992; Kalivas 1993; Dewey et al. 1992; Kalivas et al. 1992). There are GABA inhibitory afferents to dopaminergic VTA neurons (e.g., Walaas & Fonnum 1980; Yim & Mogenson 1980), inhibitory GABA interneurons within the VTA, and medium spiny GABA neurons in the nucleus accumbens that also inhibit mesolimbic dopamine release (for review, Kalivas et al. 1992). Accordingly, enhancement of GABAergic transmission abolished both dopamine increases in the nucleus accumbens and the reinforcing effects of drugs of abuse, including those induced by nicotine (Dewey et al. 1999). Specifically, systemic injections of γ-vinyl GABA (GVG, also referred to as vigabatrin, an irreversible inhibitor of GABA transaminase, the primary enzyme involved in GABA metabolism; Jung et al. 1977; Lippert et al. 1977) that leads to increased GABA levels decreased nicotine self-administration in rats (Paterson & Markou 2002), and abolished the expression and acquisition of nicotine-induced conditioned place preference (Dewey et al. 1998). Further, GVG administration dose- and time-dependently lowered the nicotine-induced increases in nucleus accumbens dopamine in both naïve and chronically nicotine-treated rats as measured by *in vivo* microdialysis, and abolished nicotine-induced increases in dopamine in the striatum of primates as measured by positron emission tomography (Krystal et al. 2002). The use of receptor-selective agonists has suggested the involvement of $GABA_B$ receptors in these effects. Systemic or microinjections of baclofen or (3-amino-2[S]-hydroxypropyl)-methylphosphinic acid (CGP44532), two $GABA_B$ receptor agonists, systemically or directly into the nucleus accumbens shell, VTA or peduncular pontine nucleus, but not into the caudate-putamen, decreased the reinforcing effects of nicotine (Shoaib et al. 1998; Corrigall et al. 2000, 2001; Fattore et al. 2002; Paterson et al. 2003). Taken together, these results suggest that enhancement of GABA transmission through activation of $GABA_B$ receptors may block the reinforcing effects of nicotine. Interestingly, however, a human clinical study showed that a

single acute dose of baclofen had no effect on either the number of cigarettes smoked or craving for nicotine (Cousins et al. 2001). Nevertheless, other clinical studies using chronic administration of baclofen showed that baclofen reduced cocaine and alcohol abuse, and cue-induced brain activation (Ling et al. 1998; Addolorato et al. 2000, 2002a, b; Childress et al. 2002). Therefore, it is possible that chronic treatment with these GABAergic drugs is required before tobacco smoking is decreased.

Acute nicotine exposure has effects also on the hypothalamic-pituitary-adrenal (HPA) axis in rodents and humans that are hypothesized to be mediated by corticotropin-releasing factor (CRF) transmission in the paraventricular nucleus of the hypothalamus. In humans, two regular strength cigarettes (equivalent to 2 mg of nicotine) or intravenous nicotine increased corticosterone and adrenocorticotropic hormone (ACTH) levels (Wilkins et al. 1982; Seyler et al. 1984; Stalke et al. 1992; Newhouse et al. 1990). Similarly, rats injected with nicotine (Cam et al. 1979; Andersson et al. 1983; Conte-Devolx et al. 1985) or exposed to inhalation of cigarette smoke showed increased levels of ACTH and corticosterone; this effect is mediated by central, but not peripheral nAchRs (Matta et al. 1987). Specifically, it was shown that the nAchR antagonist mecamylamine injected into the nucleus of the solitary tract prevented this brainstem nucleus from releasing norepinephrine into the paraventricular nucleus which in turn prevented HPA axis activation; this effect was not seen when mecamylamine was injected directly into the paraventricular nucleus (Matta et al. 1993). Several lines of evidence suggest that CRF in the paraventricular nucleus mediates the effects of nicotine on the HPA stress response system. Nicotine induces CRF release *in vitro* from both the rat hypothalamus (Hillhouse & Milton 1989) and a cell line derived from rat amygdala (Kasckow et al. 1999). Further, nAChRs are co-localized with CRF-positive vesicles on axon terminals in the paraventricular nucleus, demonstrating that nicotine could act directly on hypothalamic neurons to release CRF (Okuda et al. 1993). Finally, nicotine treatment induced c-fos protein expression in CRF-positive neurons in several brain areas, including the paraventricular nucleus (Valentine et al. 1996), bed nucleus of the stria terminalis, central nucleus of the amygdala, and the dorsal raphe (Matta et al. 1997), indicating that CRF may play a role in mediating the effect of nicotine on behaviors relating to stress and anxiety.

Finally, opioid receptor antagonists such as naloxone and naltrexone have been reported to modulate cigarette consumption and have been used as smoking cessation aids (Karras & Kane 1980; Wewers et al. 1998; Covey et al. 1999; but see Nemeth-Coslett & Griffiths 1986; Sutherland et al. 1995) suggesting that opioid receptors also may modulate the reinforcing effects of nicotine.

Adaptations in nAchR Function

Chronic nicotine administration leads to an interesting paradoxical change in the function of nAchRs that consists of receptor desensitization leading to a receptor upregulation (Marks et al. 1983; Schwartz & Kellar 1983; Changeux et al. 1984; Wonnacott 1990; Flores et al. 1997; Perry et al. 1999; Mansvelder et al. 2002). There have been complex theoretical speculations about the role of nAchR desensitization and upregulation in the subjective effects of acute nicotine, and in the development and maintenance of nicotine dependence (Marks et al. 1992; Dani & Heinemann 1996; Dani et al. 2000; Quick & Lester 2002; Buisson & Bertrand 2002). Experimental evidence indicates that long-term exposure to nicotine induces an increase in the number (Buisson & Betrand 2001; Marks et al. 1992; Wonnacott 1990) and function (Rowell & Wonnacott 1990) of nAchRs. Nevertheless, this finding is not consistent, and others see a decrease in nAchR number (Gentry et al. 2003) and function (Marks et al. 1993) with chronic exposure to nicotine. Further, behavioral findings are most readily explained by decreased number and/or function of nAchRs with the development of nicotine dependence (Epping-Jordan et al. 1998; Watkins et al. 2000b; Markou & Paterson 2001; Skjei & Markou 2003) that develop to counteract the continuous agonist actions of nicotine on the receptors. Most studies reporting changes in nAchR number and function have been conducted in *in vitro* experimental systems, and it is acknowledged that the functional significance of these changes *in vivo* are unknown (Buisson & Bertrand 2002) and need to be explored (Kellar et al. 1999). Further, it is known that different subtypes of nAchRs desensitize and upregulate at different rates which may explain the seemingly opposite effects seen in some cases (Kellar et al. 1999; Levin 2002; Buisson & Bertrand 2002). Thus, behaviorally we observe the net effect of these complex adaptations in different receptor types and brain sites. Adaptations in nAchR number and function may be long-lasting and may contribute to the difficulty many people have in achieving and sustaining nicotine abstinence even after the overt signs of nicotine withdrawal have subsided (see below). Although many smokers attempt to quit smoking and may be successful early on, only 20% of these individuals are still abstinent after one year (Hunt et al. 1971; Hunt & Bespalec 1974; Hughes et al. 1991a, b, 1992). These adaptations in nAchRs are likely to also mediate the rapid and high degree of tolerance seen to several of the effects of acute nicotine (Langley 1905; Royal College of Physicians of London 2000). Some degree of tolerance is gained also during each day of smoking and lost during the approximately 8 hours of tobacco deprivation during sleeping hours (Swedberg et al. 1990). The time course of gain and loss of tolerance varies across nicotine-induced responses (Collins & Marks 1989; Balfour & Fagerstrom, 1996; Royal College of Physicians of London 2000), with a large degree of tolerance to the subjective and cardiovascular effects of nicotine (Soria et al. 1996; USDHHS 1988; Royal College of Physicians of London 2000; Heishman & Henningfield 2000).

Neurosubstrates of Nicotine Withdrawal

Smoking cessation leads to an aversive withdrawal syndrome in humans (Hughes et al. 1991b; Shiffman & Jarvik 1976), components of which are exhibited for 1-10 weeks post-smoking (Hughes 1992). This syndrome arises, at least in part, because of the cessation of administration of nicotine through tobacco smoking. The fact that cessation of nicotine administration leads to this syndrome is suggested by the fact that the withdrawal signs can be mitigated largely by administration of pure nicotine in a variety of forms (e.g., gum, patch, nasal delivery; Shiffman et al. 1998; Heishman et al. 1994; Pickworth et al. 1995; Hughes et al. 1990). Conversely, reduction of the nicotine content in smoked tobacco induced a withdrawal syndrome in smokers that was accompanied by a significant reduction in plasma nicotine levels (West et al. 1984). This nicotine withdrawal syndrome is comprised of "physical" or somatic, affective and cognitive components. The most common somatic symptoms include bradycardia and gastrointestinal discomfort. Affective symptoms primarily include depressed mood, dysphoria, craving, anxiety and irritability. A cognitive symptom of withdrawal is difficulty concentrating, while yet another symptom is increased appetite (American Psychiatric Association 1994; Hughes et al. 1991b; West et al. 1991; Glassman et al. 1990; Parrott 1993).

Several rodent models have been developed that serve to investigate the neurobiology of nicotine withdrawal and potentially evaluate medications for treating withdrawal. One of the first and most widely used measures of nicotine withdrawal in rodents is the measurement of the frequency of somatic sings. These signs are reliably seen in rats, but are less reliably observed in mice (Malin et al. 1992, 1994; Hildebrand et al. 1997; Epping-Jordan et al. 1998; Isola et al. 1999; Carboni et al. 2000; Semenova et al. 2003). The most prominent signs of the rat withdrawal syndrome include abdominal constrictions (writhes), gasps, ptosis, facial fasciculation, and eyeblinks, while miscellaneous other signs, such as escape attempts, foot licks, genital grooming, shakes, scratches and yawns are rarely observed (Malin et al. 1998; Hildebrand et al. 1997; Watkins et al. 2000b; Cryan et al. 2003). These somatic signs are both centrally and peripherally mediated (Malin et al. 1997; Hildebrand et al. 1997; Watkins et al. 2000a; Carboni et al. 2000). Although the somatic components of nicotine withdrawal are certainly unpleasant, it is hypothesized that avoidance of the affective components of withdrawal plays a more important role in the maintenance of nicotine dependence than the somatic aspects of withdrawal (Watkins et al. 2000b; Kenny & Markou 2001; Hughes 1992). Other rodent models that may be of relevance to disruption of behavioral performance in humans involve nicotine abstinence-induced disruptions of food-maintained learned behaviors in rats (Carroll et al. 1989), increases in the acoustic startle response in rats (Helton et al. 1993), and decreased prepulse inhibition in mice (Semenova et al. 2003). A critical measure of the affective and motivational aspects of drug withdrawal is elevations in brain reward thresholds observed after cessation of chronic nicotine

administration (Epping-Jordan et al. 1998; Harrison et al. 2001; Semenova & Markou 2003; Skjei & Markou 2003; Cryan et al. 2003). Elevations in brain reward thresholds are considered to be an operational measure of "diminished interest or pleasure" in rewarding stimuli that is a symptom of nicotine withdrawal (American Psychiatric Association 1994; Covey et al. 1997). Similar reward threshold elevations are seen during withdrawal from all major drugs of abuse, such as cocaine (Markou & Koob 1991, 1992; Markou et al. 1992; Baldo et al. 1999; Kokkinidis et al. 1980; Frank et al. 1992), ethanol (Schulteis et al. 1995), morphine (Schulteis et al. 1994), amphetamine (Lin et al. 1999, 2000; Paterson et al. 2000; Harrison et al. 2001; Semenova & Markou 2003; Kokkinidis et al. 1980) and phencyclidine (Spielewoy & Markou 2003). Interestingly, several dissociations have been observed between the threshold elevations and the somatic signs associated with nicotine withdrawal (Watkins et al. 2000b; Harrison et al. 2001; Semenova & Markou 2003), suggesting that the various aspects of withdrawal are mediated by different substrates.

Although the substrates of nicotine withdrawal have not been investigated as extensively as the substrates of the reinforcing effects of acute nicotine, there are studies suggesting that adaptations in the circuits mediating the acute effects of nicotine occur with the development of nicotine dependence that lead to the withdrawal syndrome. During nicotine withdrawal precipitated by systemic or intra-VTA administration of the nAchR antagonist mecamylamine in nicotine-treated rats, dopamine dialysate levels were decreased in the nucleus accumbens (Fung et al. 1996; Hildebrand et al. 1998; Carboni et al. 2000) and the central nucleus of the amygdala (Panagis et al. 2000). These mecamylamine injections into the VTA also produced dose-dependently most of the somatic signs of nicotine withdrawal (Hildebrand et al. 1999), suggesting the possible involvement of nAchRs transmission in the VTA in the expression of the somatic signs of nicotine withdrawal. Similar decreases in nucleus accumbens dopamine levels are associated also with withdrawal from other drugs of abuse, such as ethanol, morphine, cocaine and amphetamine (e.g., Rossetti et al. 1992; Weiss et al. 1992). By contrast, increases in dialysate dopamine levels were observed in the frontal cortex (Carboni et al., 2000; however, see Hildebrand et al. 1998), similar to those seen during withdrawal from other drugs of abuse (Acquas & Di Chiara 1992; Bassareo et al. 1995). It is noteworthy that the smoking cessation aid bupropion (an atypical antidepressant; trade name Zyban or Wellbutrin) acts, at least in part, by inhibiting neuronal uptake of dopamine and thereby enhancing dopamine transmission (Terry & Katz 1997; Nomikos et al. 1992). Bupropion has been shown to reverse both the threshold elevations and the somatic signs associated with nicotine withdrawal (Cryan et al. 2003; Malin 2001), while its effects on nicotine self-administration are inconsistent (Shoaib et al. 2002; Glick et al. 2002; Bruijnzeel & Markou 2003).

Considering that these decreases in nucleus accumbens dialysate levels are induced by administration of nAchR antagonists into the VTA, it is suggested that a reduction in endogenous cholinergic tone leads to this effect. The types of nAchRs involved probably include the α4-containing high-affinity nAChRs (Harvey & Luetje 1996; Damaj et al. 1995; Harvey et al. 1996; Wonnacott 1997; Epping-Jordan et al. 1998) but not the α7 nAChRs (Markou & Paterson 2001). Administration of the α7 nAchR antagonist methyllycaconitine did not precipitate either somatic signs or threshold elevations in nicotine-dependent rats suggesting that these receptors may not be involved in the development of nicotine dependence, despite the fact that α7 receptors undergo rapid desensitization in the presence of concentrations of nicotine achieved in the brains of smokers (Alkondon et al. 2000; Pidoplichko et al. 1997).

Serotonin (5-HT), and the 5-HT_{1A} receptor in particular, also appear to play a role in nicotine withdrawal (Benwell et al. 1990; Kenny et al. 2001). Systemic administration of 5-HT_{1A} receptor agonists such as 8-OH-DPAT exacerbated the increased startle response observed during nicotine withdrawal, whereas 5-HT_{1A} receptor antagonists, such as WAY-100635, alleviated this enhanced response (Rasmussen et al. 1997; 2000). Further, the responsiveness to 8-OH-DPAT of dorsal raphe nucleus neurons was increased during nicotine withdrawal (Rasmussen & Czachura 1997). Thus, nicotine withdrawal may increase the inhibitory influence of somatodendritic 5-HT_{1A} autoreceptors located within the raphe nuclei and thereby decrease 5-HT release into forebrain and limbic brain sites (e.g. Benwell & Balfour 1979, 1982a; Ridley & Balfour 1997). This conclusion is supported by the observation that a serotonergic antidepressant treatment involving the co-administration of the selective serotonin reuptake inhibitor fluoxetine and the 5-HT_{1A} receptor antagonist p-MPPI rapidly reversed the elevation in brain-stimulation reward thresholds observed in rats undergoing nicotine withdrawal but did not block the somatic signs of withdrawal (Harrison et al. 2001). These data provide further evidence for a dissociation of the mechanisms mediating affective and somatic aspects of nicotine withdrawal. Consistent with the above, the 5-HT_{1A} receptor partial agonist buspirone shows efficacy in smoking cessation trials and may reduce withdrawal severity in abstinent smokers (Hilleman et al. 1992, 1994; West et al. 1991; but see Schneider et al. 1996).

Another transmitter system likely to be involved in nicotine withdrawal is glutamate, considering the role of glutamate in the reinforcing effects of nicotine (see above). Based on the stimulatory effects of glutamate neurotransmission on dopamine release (Mansvelder & McGehee 2000; Schilstrom et al. 1998a), it may be hypothesized that decreased glutamate transmission mediates nicotine withdrawal. Indeed, increased glutamate transmission via antagonism of presynaptic inhibitory Group II metabotropic glutamate receptors (for review, see Cartmell & Schoepp, 2000) reversed the affective aspects of nicotine withdrawal (Kenny et al. 2003). Nevertheless, an agonist at Group II metabotropic glutamate receptors that decreases glutamate

transmission ameliorated the increased startle response seen in rats undergoing nicotine withdrawal (Helton et al. 1997). This result suggests that either decreased or increased glutamate transmission is involved in different aspects of nicotine withdrawal. Further studies are warranted to further investigate the role of glutamate in various aspects of nicotine withdrawal in different brain sites.

In terms of the CRF system and the HPA axis, generally smokers have elevated levels of plasma cortisol (Kirschbaum et al. 1992; Frederick et al. 1998) that do not change significantly within the first several days of quitting smoking (Pickworth et al. 1996; Benowitz et al. 1984; Teneggi et al. 2002) but decline after several weeks of abstinence (Puddey et al. 1984; Frederick et al. 1998). Further, there is rapid tolerance to the effects of nicotine on plasma corticosterone (Benwell & Balfour 1979; Cam & Bassett 1984; Sharp and Bayer 1986). During nicotine withdrawal, both increases and decreases in corticosterone levels have been reported in experimental subjects (Benwell & Balfour 1982b; Rasmussen 1998; Andersson et al. 1989). Further research is warranted to best characterize the effects of nicotine withdrawal in CRF transmission and HPA axis function.

Finally, the opioid system also may be involved in nicotine withdrawal. The opioid receptor agonist morphine reversed withdrawal signs in rats undergoing spontaneous nicotine withdrawal (Malin et al. 1993), while nicotine reduced naloxone-precipitated opiate withdrawal in rats (Zarrindast & Farzin 1996). Further, μ opioid receptor knockout mice do not show nicotine place preference or nicotine withdrawal (Berrendero et al. 2002). These results suggest that common neurobiological substrates may mediate nicotine and opiate withdrawal. Accordingly, naloxone and an analog of the endogenous antiopiate, neuropeptide FF, precipitated somatic withdrawal signs after chronic nicotine treatment (Malin et al. 1993, 1996; Carboni et al. 2000; however, see Watkins et al. 2000b) but only with extremely high naloxone doses (Carboni et al. 2000; Malin et al. 1993) compared to those required to precipitate withdrawal in opioid-dependent rats (Gellert & Sparber 1977; Brady & Holtzman 1981; Koob et al. 1989; Higgins & Sellers 1994; Schulteis et al. 1994). Further, naloxone injections did not differentially elevate brain reward thresholds in nicotine- and saline-treated rats (Watkins et al. 2000b). By contrast, low naloxone doses led to conditioned place aversions in nicotine-dependent rats (Ise et al., 2000; Watkins et al. 2000b). Overall, this pattern of results suggests that somatic withdrawal signs and brain reward thresholds are not particularly sensitive to alterations in opioid transmission, while conditioned motivational states may be. Interestingly, both naloxone (Tome et al. 2001) and naltrexone (Almeida et al. 2000) recently have been shown to antagonize nAChRs, suggesting that opioid receptor antagonists may precipitate nicotine withdrawal, at least in part, by directly blocking nAChRs.

Chronic Nicotine, Opponent Process, Allostasis and the Development of Dependence

There are similarities and differences between nicotine and other major drugs of abuse. Although nicotine is an effective reinforcer in animal models, when compared directly to other drugs of abuse such as cocaine, nicotine appears to have less reinforcing efficacy in nondependent animals (Risner & Goldberg, 1983). The paradox, however, is that chronic administration of nicotine produces a robust dependence from the perspective of disruption of brain reward systems. Brain reward thresholds in rats are elevated for periods up to a month with chronic nicotine exposure (Skjei & Markou 2003), probably reflecting a protracted dysphoric state, similarly to the one that leads to relapse in humans. To date there is little or no evidence of an increase in the efficacy of nicotine as a reinforcer in animal models after chronic administration of nicotine sufficient to dramatically alter reward thresholds, but such studies remain to be conducted.

From a motivational perspective, such a shift in reward processing may reflect changes in the dynamics of the reward system associated with opponent and allostatic mechanisms. Solomon and Corbit (1974) postulated that hedonic, affective or emotional states, once initiated, are automatically modulated by the central nervous system with mechanisms that reduce the intensity of hedonic feelings. Termed the opponent-process theory of motivation, Solomon argued that there is affective or hedonic habituation (or tolerance) and affective or hedonic withdrawal (abstinence). More specifically, an *a-process*, which could be either a positive or negative hedonic response, was proposed to 1) occur shortly after presentation of a stimulus, 2) correlate closely with the stimulus intensity, quality and duration of the reinforcer, and 3) show tolerance. In contrast, the *b-process* was proposed 1) to appear after the *a-process* terminated and be slow in onset, 2) to be slow to build up to asymptote and slow to decay, and 3) to get larger with repeated exposure.

From a neurobehavioral perspective it was hypothesized that in brain motivational systems the initial acute effect of an emotional stimulus or drug is opposed or counteracted by homeostatic changes in brain systems. This affect control system was conceptualized as a single negative feedback or an opponent loop that opposes the stimulus-aroused affective state (Solomon & Corbit, 1974; Siegel, 1975; Poulos & Cappell, 1991). In the context of drug dependence, Solomon argued that the first few self-administrations of an opiate drug produce a circumscribed pattern of motivational changes. The onset of the drug effect produces euphoria that is the *a-process*, and this euphoria is followed by a decline in its intensity. Then after the drug wears off, a *b-process* state emerges as an aversive craving state.

More recently, opponent process theory has been expanded into the domains of the neurocircuitry and neurobiology of drug addiction from a physiological perspective (Koob & Le Moal, 2001). An allostatic model of the brain motivational systems was proposed that explains

the persistent changes in motivation that are associated with vulnerability to relapse in addiction. *Allostasis* is defined as the maintenance of stability outside of the normal homeostatic range, where an organism must vary all the parameters of its physiological systems to match them appropriately to chronic demands (e.g., reset the system parameters at a new set point; Sterling & Eyer 1988). Thus, allostasis refers to the integrative adaptive processes maintaining stability through change, a stability that is not within the normal homeostatic range. In this framework, addiction is conceptualized as a continuous dysregulation of brain reward systems that progressively increases resulting in compulsive drug use. Counteradaptive processes such as opponent-process that are part of the normal homeostatic limitation of reward function fail to return within the normal homeostatic range and are hypothesized to form an allostatic state. An allostatic state can be defined as a state of chronic deviation of the regulatory systems from their normal state of operation with establishment of a new set point. This allostatic state that is hypothesized to be reflected in a chronic deviation of the reward set point is fueled not only by dysregulation of reward circuits per se, but also by recruitment of brain and hormonal stress responses.

In terms of nicotine dependence, nicotine, like other drugs of abuse may be hypothesized to drive the brain reward system into an allostatic state. Atlhough there is a less dramatic *a-process* than with other drugs of abuse, there appears to be a protracted *b-process* with nicotine. At least two neurobiological hypotheses can be generated to explain an opponent process/allostatic view of nicotine addiction. At the molecular level, Dani and Heinemann (1996) proposed a desensitization model where nicotine stimulates the mesolimbic dopamine system via activation of nAchRs to produce the reinforcing effects of acute nicotine, but with continued use the inactivation of these receptors by desensitization leads to adaptive tolerance. During abstinence, nicotine levels fall, and the increased number of nAchRs throughout the brain begin to recover to a responsive state that may be dependent on the nAchR subtype. Engaging nAchRs in non-reward-related pathways could contribute to the aversive emotional states associated with nicotine withdrawal. According to this hypothesis, smokers in effect would be ultimately medicating themselves with nicotine to regulate the number of functional nAchRs (Dani & Heinemann, 1996). Recent work shows that such changes may be evident in the α subunit family, with the $\alpha 4$, $\alpha 2$ and $\alpha 7$ subunits showing inactivation with chronic nicotine, but the $\alpha 3$ subunit (which is similar in structure to the $\alpha 6$ subunit) showing resistance to desensitization (Olale et al. 1997). Thus, one could speculate that there are two powerful forces for development of nicotine addiction at the receptor level: desensitization of nAchRs in non-reward pathways (that leads to self-medication with nicotine), and resistance to desensitization in reward pathways (positive reinforcement).

An alternative hypothesis at the neurobiological level of analysis is that chronic nicotine exposures "deplete" neurotransmitter systems implicated in the reinforcing effects of nicotine and reward in general. Decreases in dopamine, opioid peptides, serotonin and glutamate all have been observed following chronic nicotine exposure (see above). Brain sites hypothesized to be implicated in these neurochemical dysregulations would include elements of the ventral midbrain such as the VTA and the extended amygdala (central nucleus of the amygdala, bed nucleus of the stria terminalis, and medial nucleus accumbens). However, with other drugs of abuse, a second powerful neurochemical dysregulation of the brain motivational systems has been implicated in the allostatic changes associated with the development of dependence (e.g., recruitment of activity in the hormonal and brain stress systems). Nicotine may be unique in that there is little evidence of a robust activation of the HPA axis response to stress during withdrawal from nicotine, yet there are behavioral signs of anxiety in humans and anxiety-like responses in animal models (Pickworth et al. 1996). How the brain stress systems acting in the brain independent of the HPA axis (such as CRF and neuropeptide Y) respond during nicotine dependence is a challenge for future research.

In summary, nicotine is a somewhat unique drug of abuse in that it produces only a relatively small reinforcing effect acutely, but it certainly has high dependence-inducing efficacy. This dissociation suggests that nicotine may be selectively potentiating some part of the motivational systems associated with opponent processes leading to an allostatic disruption of reward function. Desensitization of brain nAchRs at the molecular level, depletion of brain reward neurotransmitters and disruption of brain stress systems are hypothesized to contribute to such an allostatic state.

POLICY IMPLICATIONS FOR TOBACCO CONTROL

The understanding that tobacco dependence has a pathophysiological basis, which has been increasingly elucidated by advances in understanding the neurobiological mechanisms of nicotine reinforcement and dependence, has implications for tobacco control efforts. Additionally, this understanding strengthens the rationale for comprehensive tobacco programs that emphasize prevention and cessation efforts; just as understanding that the disease of malaria is caused by a mosquito-carried parasite strengthens the importance of comprehensive efforts to prevent exposure, and treat those afflicted to the greatest extent possible.

Prevention

Prevention of tobacco use is critically important because exposure to tobacco is not an innocuous behavior but rather a behavior that triggers a cascade of neurobiological events which can, in turn, affect subsequent behavior. Moreover, each subsequent exposure to tobacco leads to the establishment of tolerance, physiological dependence and a potential strengthening of the

biologically rewarding effects of nicotine. This cascade of events can lead to increased daily self-administration and progression of the dependence process. It is not known if all nicotine-induced changes in brain function, such as 300% increases in nAchR numbers in some brain regions (Perry et al. 1999), and alterations of brain nicotine reinforcement systems (Mansvelder et al. 2002), are fully reversed after nicotine abstinence in all persons. It is plausible that persisting alterations may confer a continuing need for nicotine in some individuals (Henningfield & Slade 1998). Because dependence occurs on a continuum of severity, efforts should be made to divert the usual trajectory of increased tobacco use away from the course to addiction as early as possible to prevent severe addiction from being established. Making every effort to prevent any use, as well as to prevent the development of severe addiction in those who do initiate use, is especially important in developing countries where resources for treating severely addicted tobacco users may be very limited.

Evidence indicates that while all adults are susceptible to the biological effects of tobacco, it also appears plausible that earlier onset of use is associated with a higher risk of developing dependence. Therefore, if the population goal is reduced prevalence of tobacco use, then efforts should be made to discourage initiation of use by persons of all ages (Henningfield et al. 2003). The possibility that substances in tobacco products and tobacco smoke contribute to addiction (Royal College of Physicians of London 2000; Henningfield & Zeller 2003) increases concerns about the risks of tobacco exposure. An additional concern is efforts claiming to reduce the risks of heavy tobacco use by the promotion of products assumed to be less toxic (e.g., Bates et al. 2003), because such promotion carries the risk of undermining prevention and cessation efforts (Henningfield & Fagerstrom 2001; Henningfield et al. 2002, 2003).

Cessation

The major implication of understanding that there is a pathophysiological basis for tobacco addiction also may be considered analogous to the understanding that there is a physiological basis for malaria. Specifically, this understanding implies that although some severely addicted people will be able to achieve lasting cessation without medicine, others may require medicines to enable their nervous and endocrine systems to function satisfactorily in the absence of tobacco-delivered nicotine. It also implies that there are physiological targets through which medications can exert effects that would aid cessation, and that some people may require that the physiological aspects of addiction be treated if they are to sustain cessation.

It is clear that many people can achieve cessation without formal treatment intervention and this is encouraging for developed and developing countries alike. Unfortunately, it is equally clear that many people, particularly heavier tobacco users who are also at greater risk of disease, are unable to sustain cessation without treatment (USDHHS 2000; Royal College of Physicians of

London 2000; Fiore et al. 2000). Because it is not known what percentage of tobacco users require treatment to sustain cessation or which tobacco users benefit the most from specific treatments, a goal of comprehensive tobacco control should be to ensure access to a diversity of effective treatments. An implication for the development of new medications for treating tobacco dependence is that a variety of potential mechanisms have emerged as potential targets for treatment drugs. These include drugs that bind to nAchR subtypes and modulate neurohormonal systems, including those involving dopamine and other catecholamines, serotonin, GABA and glutamate.

It should be emphasized that understanding of tobacco use as a behavior involving a neurobiological driving force does not lessen the importance of non-biological determinants of tobacco addiction. Clearly, factors including social acceptability, knowledge of harmfulness, restrictions of tobacco use, cost, and accessibility affect the risk of developing and sustaining dependence, as well as the probability of cessation (USDHHS 2000; Royal College of Physicians of London 2000; Fiore et al. 2000). The above is consistent with the recommendations of the U.S. Centers for Disease Control and Prevention advocating that comprehensive tobacco control strategies address all such factors and provide access to treatment.

Pharmacotherapy – focus on smokeless tobacco

The treatment of cigarette dependence has been well studied, and a number of behavioral and pharmacologic approaches have been developed and shown to be efficacious. In contrast, much less research has been conducted on the treatment of smokeless tobacco dependence, and the approaches generally have been modeled after smoking cessation treatments. Following is a brief review of the behavioral and pharmacologic approaches that have been studied for smokeless tobacco use.

Hatsukami and Severson (1999) have reviewed the behavioral approaches that have been studied. As with smoking cessation, studies generally have shown that behavioral interventions have improved smokeless tobacco cessation rates compared to control groups with no intervention. Further, there is a dose-response relationship in that more intensive therapy tends to improve rates compared to less intensive interventions. In addition, brief advice from a health care professional can improve smokeless cessation rates, particularly in the dental setting.

There have been few studies of the efficacy of nicotine replacement medications (NRT) for the treatment of smokeless tobacco dependence. Nicotine gum would be the obvious choice of NRT formulations because it would allow the smokeless user to receive the oral stimulation and nicotine normally obtained by tobacco. However, three studies of 2 mg nicotine gum showed minimal efficacy in long-term cessation rates (Sinusas & Coroso 1993; Boyle et al. 1993; Hatsukami et al. 1996, 2000). The general lack of efficacy of the gum may be dose-related, as

there has been little published work on the efficacy of 4 mg nicotine gum on smokeless tobacco use. Moist snuff delivers at least as much nicotine during use as cigarette smoking with peak plasma nicotine levels during Copenhagen use reaching over 20 ng/ml (Fant et al. 1999). Whereas 4 mg nicotine gum would not produce the nicotine levels associated with smokeless tobacco use, it would lead to levels higher than those achieved during 2 mg use. Given that smoking cessation with nicotine gum is dose-related, one could predict that the same might be true for smokeless tobacco cessation.

The transdermal nicotine patch in theory could treat smokeless tobacco dependence by breaking the habit of oral dosing while reducing the nicotine withdrawal symptoms associated with abrupt withdrawal from smokeless tobacco use. The data thus far, however, are equivocal. One study compared transdermal nicotine and mint snuff in a 2x2 factorial design and found that the nicotine patch was effective in increasing short-term abstinence over the placebo patch, and in reducing craving and withdrawal signs and symptoms from spit tobacco. There have been no studies of other NRT formulations (e.g., nasal spray, inhaler, and lozenge). The use of lozenge would be predicted to mimic the effects of nicotine gum because the delivery of nicotine would be comparable in terms of both speed and magnitude. Hatsukami & Severson suggest that nicotine nasal spray would not be an ideal treatment option for smokeless users because the delivery of nicotine from spray would be very rapid in contrast to the slower delivery of nicotine from smokeless tobacco. The nicotine inhaler involves puffing a device that has the general appearance of a cigarette and delivers very low doses of nicotine, and thus would appear less likely to benefit smokeless users.

Two recent studies have shown bupropion to be effective for the treatment of smokeless tobacco dependence. Results from a placebo-controlled trial of 68 smokeless tobacco users indicated that at the end of 12 weeks of therapy, the point-prevalence tobacco abstinence rate was 44% in the bupropion group and 26% in the placebo group ($p < 0.07$); however, the effect was not present at 24 weeks (Dale et al. 2002). Bupropion also was associated with a reduction in nicotine withdrawal symptoms and weight gain. In the second study (N=70), bupropion produced significantly higher quit rates for smokeless tobacco cessation at the end of treatment (7 weeks) than placebo ($p < 0.05$) with an odds ratio of 2.73 (Glover et al. 2002). These results suggest that bupropion may be effective in increasing rates of abstinence among smokeless users; however, larger studies are clearly needed to confirm these findings.

In conclusion, significant advances in our understanding of the neurobiology of nicotine reinforcement, dependence and withdrawal provides us with excellent starting points on which to base our efforts to develop effective pharmacological and behavioral interventions to both prevent and treat dependence of smoked and smokeless tobacco products. Further research is needed to continue the investigations of the neurosubstrates mediating not only nicotine addiction but also

the effects of other tobacco ingredients that contribute also to the tobacco use habit, and the synergistic effects of these tobacco ingredients with nicotine that promote this deadly habit.

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